Synthesis of 6-(2-hydroxyaryl)-2-pyridones by the reaction of chromones with cyanoacetic, acetoacetic, and malonic acid amides

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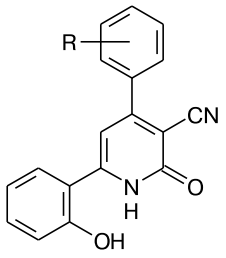
A reaction of chromones with cyanoacetic, acetoacetic, and malonic acid amides in the presence of sodium ethoxide furnished a number of new 3-substituted 6-(2-hydroxyaryl)-2-pyridones in good yields, including those containing a polyfluoroalkyl group at position 4.

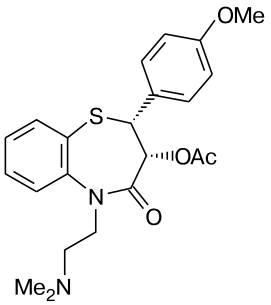
Key words: chromones, active methylene amides, 2-pyridones, R^F-containing compounds.

4-Aryl-3-cyano-6-(2-hydroxyphenyl)-2-pyridones **1** are known as compound possessing a wide range of biological activity, which exhibit antiinflammatory, antibacterial, and analgesic properties.[1] Besides, they are Pim-1 kinase inhibitors,[2] can be used in the studies of biochemical role of a unique apoptosis inhibitor survivine,[3] and can successfully compete as calcium channel blockers with such medicine of the benzothiazepine series as dilthiazem **2** (see Ref. 4).

At the same time, the introduction of a trifluoromethyl group in the bioactive molecules is an important aspect in the pharmaceutical studies, which stimulates research directed on the search and development of new methods for the preparation of CF_3-containing heterocycles. In this connection, the replacement of the 4-aryl substituent in 2-pyridones **1** with the CF_3 group is of undoubted interest as an approach to the synthesis of new 2-pyridone derivatives with potential biological activity.



1



2

Earlier, 3,6-disubstituted 4-trifluoromethyl-2-pyridones were obtained by cyclocondensation of 1-trifluoromethyl-1,3-diketones with cyanoacetamide[1,5—7] and *N*-methylcyanoacetamide,[8] whereas mono- and disubstituted 6-trifluoromethyl-2-pyridones by the reaction of cyanoacetic, acetoacetic, and malonic acid amides with 4-alkoxy-1,1,1-trifluorobut-3-en-2-ones,[9,10] 1,1,1-trifluoro-4-methoxypent-3-en-2-one,[9] and 4,4-bis(methylthio)-1,1,1-trifluorobut-3-en-2-one.[11] In the present work, we studied a reaction of 2-polyfluoroalkylchromones, unsubstituted chromone, and 2-methylchromones with active methylene amides, thus obtaining a number of new biologically active analogs of 2-pyridones **1**, including those containing polyfluoroalkyl group at position 4 (see preliminary communication[12]).

Results and Discussion

The reactions of 2-polyfluoroalkylchromones **3** with 1,3-dinucleophiles are fairly well studied.[13] The studies showed that imines and enamines resulted in the formation of R^F-containing pyridines[14,15] and benzenes,[16] whereas amidines gave pyrimidines.[14] However, there are no literature data on the reaction of 2-R^F-chromones **3** with amides having an active methylene group. As to 2-methylchromones, they depending on the conditions react with active methylene amides at both the carbonyl group, giving rise to the corresponding methylidene derivatives (1,2-addition),[17] and at atom C(2), which leads to 4-methyl-2-pyridones (1,4-addition).[18,19]

We found that 2-R^F-chromones **3** react with cyanoacetamide, *N*-methylcyanoacetamide, as well as with acetoacetic and malonic acid amides in the presence of sodium ethoxide upon reflux in ethanol for 4—6 h, giving 6-(2-hydroxyaryl)-4-polyfluoroalkyl-2-pyridones **4a—l** in 65—95% yields (the yield of pyridone **4m** from acetoacetanilide was 38%). Pyridone **4a** was also obtained from malononitrile and 2-trifluoromethylchromone in 65% yield. *N*-Ethyl- and *N*-phenylcyanoacetamides did not give this reaction, whereas the use of piperidinium acetate as the catalyst, showing good results in the reaction of cyanoacetamide with trifluorobenzoylacetone,[6] did not increase the yield. The products obtained are colored (from

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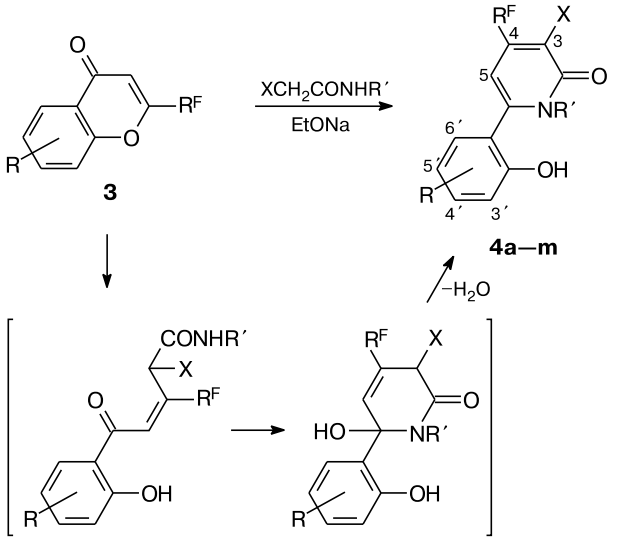
pale yellow to light brown) high-melting powders, whose structure was confirmed by elemental analysis, IR and ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. The reaction follows the mechanism of nucleophilic 1,4-addition to chromones **3** with subsequent pyrone ring opening and heterocyclization upon the attack by the amino group at the carbonyl carbon atom (Scheme 1).

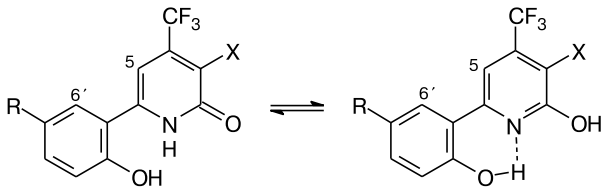
Scheme 1



4	R^F	R	R′	X	Yield (%)
a	CF_3	H	H	CN	68
b	CF_3	H	H	COMe	65
c	CF_3	5′-Me	H	COMe	74
d	CF_3	H	H	CO_2Et	85
e	CF_3	H	Me	CN	74
f	CF_3	5′-Me	Me	CN	85
g	CF_3	4′,6′-2Me	Me	CN	88
h	CF_3	5′-NO_2	Me	CN	88
i	CF_2H	5′-Me	Me	CN	95
j	CF_2H	4′-MeO	Me	CN	80
k	$(CF_2)_2H$	4′-MeO	Me	CN	78
l	C_2F_5	4′-MeO	Me	CN	75
m	CF_3	H	Ph	COMe	38

As in the case of trifluoromethylated 1,3-diketones,[1,5–8] we observed the formation of only single 4-R^F-regioisomer. The choice between 4-CF_3- and 6-CF_3-2-pyridones was made in favor of the former based on the ^{13}C NMR spectrum of compound **4e**, which exhibited the quartets for carbon atoms C(3), C(5), and C(4) at δ 97.0 ($^{3}J_{C,F}$ = = 2.2 Hz), 103.8 ($^{3}J_{C,F}$ = 4.4 Hz), and 143.9 ($^{2}J_{C,F}$ = = 33.0 Hz), respectively; all the signals were assigned based on the analysis of ^{1}H—^{13}C HSQC and HMBC 2D experiments. The ^{1}H NMR spectra of pyridones **4a—d** (R′ = H) in DMSO-d_6 are characterized by the presence of very broad singlets for protons H(5) and H(6′), that indicates a slow in the NMR spectroscopy time scale prototropic tautomerism between the 2-pyridone (**4**) and 2-hydroxypyridine (**4′**) forms (Scheme 2).

Scheme 2

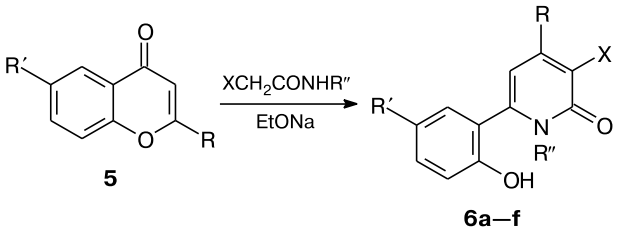


4a—d **4′a—d**

The latter tautomer is more preferable, since due to the formation of the intramolecular hydrogen bond (IMHB) between the phenol hydroxyl and the pyridine nitrogen atom both aromatic rings are placed in one plane, that results in the deshielding the proton H(6′) (δ ~ 7.6). In contrast to *N*-unsubstituted 2-pyridones **4a—d**, the phenol ring in compounds **4e—m** (R′ = Me, Ph) deviates from the plane of the molecule because of steric hindrance, which results in the upfield shift of the signal for proton H(6′) (δ 7.0—7.3). The pyridone proton H(5) in this compounds is observed as a sharp singlet in the region δ 6.4—6.7, whereas the singlet of the CF_3 group in the ^{19}F NMR spectra is found around δ –64 for 3-cyano-substituted and δ –61 for 3-acetyl and 3-ethoxycarbonyl derivatives, that corresponds to 4-CF_3-2-pyridones[7,20] (in 6-CF_3-2-pyridones, this group is in the region δ –67[11,20]).

Taking into account that 3-cyano-6-(2-hydroxyphenyl)-2-pyridones **1** exhibit various types of biological activity and are of great interest for medicinal chemistry,[1–4] we extended the reaction with active methylene amides to the unsubstituted chromone, as well as obtained a number of new 4-methyl-2-pyridones with 2-hydroxyaryl substituent at position 6 from 2-methyl- and 2-methyl-6-nitrochromones **5**. It was found that the reaction of these compounds with cyanoacetamide, *N*-methylcyanoacetamide, and malonic acid diamide in the presence of sodium ethoxide in ethanol afforded pyridones **6a—f** in 32—71% yields, whose structure is in good agreement with the elemental analysis data and the ^{1}H NMR spectra (Scheme 3).

Scheme 3



6	R	R′	R″	X	Yield (%)
a	H	H	H	CN	60
b	H	H	Me	CN	47
c	H	H	H	$CONH_2$	32
d	Me	NO_2	H	CN	71
e	Me	NO_2	Me	CN	69
f	Me	H	H	$CONH_2$	37

Note that flavone did not react with cyanoacetamide under similar conditions. The regiochemistry of the products obtained from 2-methylchromones was confirmed earlier.[19]

In conclusion, the behavior of 2-polyfluoroalkylchromones and unsubstituted chromone in the reaction with active methylene amides is similar to that of 2-methylchromones studied earlier: the reaction gives a number of new 6-(2-hydroxyaryl)-2-pyridones with high regioselectivity and good yields.

Experimental

IR spectra were obtained on a Bruker Alpha FTIR spectrometer using a frustrated total internal reflection (FTIR) appliance (ZnSe-crystal). ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on Bruker DRX-400 and Bruker Avance II spectrometers (400, 376 and 100 MHz, respectively) in DMSO-d_6, using Me_4Si and $CFCl_3$ as internal standards. Elemental analysis was performed on a PE 2400 automatic analyzer. Chromones **3** were obtained according to the known procedure.[21]

Synthesis of pyridones 4 and 6 (general procedure). Chromone **3** or **5** (3.0 mmol) and the corresponding amide (3.6 mmol) were added to a solution of sodium ethoxide prepared from sodium (83 mg, 3.6 mmol) in anhydrous ethanol (10 mL). The mixture obtained was refluxed for 4—6 h, then the orange reaction mixture formed was cooled to ~20 °C, acidified with 3 *M* aqueous hydrochloric acid (25 mL), diluted with water to 75 mL, and allowed to stand for 16 h at room temperature or in a refrigerator. A precipitate formed was filtered off, washed with reflux aqueous ethanol or recrystallized from aqueous ethanol (from acetonitrile for **4d**).

6-(2-Hydroxyphenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (4a). The yield was 68%, yellow crystals, m.p. 317—318 °C. Found (%): C, 55.70; H, 2.33; N, 9.97. $C_{13}H_7F_3N_2O_2$. Calculated (%): C, 55.72; H, 2.52; N, 10.00. IR, ν/cm^{-1}: 3403, 3145, 2227, 1659, 1645, 1605, 1576, 1551. ^{1}H NMR (DMSO-d_6), δ: 6.92 (t, 1 H, H(5′), *J* = 7.5 Hz); 6.98 (d, 1 H, H(3′), *J* = 8.3 Hz); 6.9—7.3 (br.s, 1 H, H(5)); 7.34 (ddd, 1 H, H(4′), *J* = 8.3 Hz, *J* = 7.5 Hz, *J* = 1.5 Hz); 7.63 (br.s, 1 H, H(6′)); 10.4—11.2 (br.s, 1 H, OH); 12.8—13.4 (br.s, 1 H, NH/OH). ^{19}F NMR (DMSO-d_6), δ: −63.9 (s, CF_3).

3-Acetyl-6-(2-hydroxyphenyl)-4-trifluoromethylpyridin-2(1*H*)-one (4b). The yield was 65%, pale yellow crystals, m.p. 256—257 °C. Found (%): C, 56.61; H, 3.39; N, 4.76. $C_{14}H_{10}F_3NO_3$. Calculated (%): C, 56.57; H, 3.39; N, 4.71. IR, ν/cm^{-1}: 3178, 1709, 1625, 1599, 1551. ^{1}H NMR (DMSO-d_6), δ: 2.48 (s, 3 H, Me); 6.5—7.2 (br.s, 1 H, H(5)); 6.87 (td, 1 H, H(5′), *J* = 7.5 Hz, *J* = 0.9 Hz); 6.94 (d, 1 H, H(3′), *J* = 8.1 Hz); 7.27 (ddd, 1 H, H(4′), *J* = 8.1 Hz, *J* = 7.5 Hz, *J* = 1.5 Hz); 7.58 (br.s, 1 H, H(6′)); 10.0—11.0 (br.s, 1 H, OH); 12.1—12.7 (br.s, 1 H, NH/OH). ^{19}F NMR (DMSO-d_6), δ: −60.8 (s, CF_3).

3-Acetyl-6-(2-hydroxy-5-methylphenyl)-4-trifluoromethylpyridin-2(1*H*)-one (4c). The yield was 74%, yellow crystals, m.p. 266—267 °C. Found (%): C, 57.82; H, 3.68; N, 4.45. $C_{15}H_{12}F_3NO_3$. Calculated (%): C, 57.88; H, 3.89; N, 4.50. IR, ν/cm^{-1}: 3152, 1708, 1631, 1591, 1536, 1509. ^{1}H NMR (DMSO-d_6), δ: 2.26 (s, 3 H, Me); 2.49 (s, 3 H, MeCO); 6.6—7.0 (br.s, 1 H, H(5)); 6.88 (d, 1 H, H(3′), *J* = 8.3 Hz); 7.15 (dd, 1 H, H(4′), *J* = 8.3 Hz, *J* = 2.0 Hz); 7.44 (br.s, 1 H, H(6′)); 10.0—10.8 (br.s, 1 H, OH); 12.2—12.7 (br.s, 1 H, NH/OH). ^{19}F NMR (DMSO-d_6), δ: −60.7 (s, CF_3).

Ethyl 6-(2-hydroxyphenyl)-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carboxylate (4d). The yield was 85%, pale yellow crystals, m.p. 202—204 °C. Found (%): C, 54.82; H, 3.87; N, 4.30. $C_{15}H_{12}F_3NO_4$. Calculated (%): C, 55.05; H, 3.70; N, 4.28. IR, ν/cm^{-1}: 3155, 2988, 1740, 1625, 1584, 1556. ^{1}H NMR (DMSO-d_6), δ: 1.33 (t, 3 H, Me, *J* = 7.1 Hz); 4.31 (q, 2 H, CH_2, *J* = 7.1 Hz); 6.88 (td, 1 H, H(5′), *J* = 7.4 Hz, *J* = 0.8 Hz); 6.94 (d, 1 H, H(3′), *J* = 8.1 Hz); 6.9—7.2 (br.s, 1 H, H(5)); 7.28 (ddd, 1 H, H(4′), *J* = 8.1 Hz, *J* = 7.4 Hz, *J* = 1.5 Hz); 7.62 (br.s, 1 H, H(6′)); 10.4—11.7 (br.s, 1 H, OH); 12.2—12.6 (br.s, 1 H, NH/OH). ^{19}F NMR (DMSO-d_6), δ: −62.2 (s, CF_3).

6-(2-Hydroxyphenyl)-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (4e). The yield was 74%, light brown crystals, m.p. 221—222 °C. Found (%): C, 57.02; H, 3.43; N, 9.50. $C_{14}H_9F_3N_2O_2$. Calculated (%): C, 57.15; H, 3.08; N, 9.52. IR, ν/cm^{-1}: 3151, 2232, 1634, 1601, 1571, 1557. ^{1}H NMR (DMSO-d_6—CCl_4), (2 : 3), δ: 3.40 (s, 3 H, Me); 6.47 (s, 1 H, H(5)); 6.94 (td, 1 H, H(5′), *J* = 7.5 Hz, *J* = 1.0 Hz); 6.99 (d, 1 H, H(3′), *J* = 8.3 Hz); 7.23 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.6 Hz); 7.36 (ddd, 1 H, H(4′), *J* = 8.3 Hz, *J* = 7.5 Hz, *J* = 1.6 Hz); 10.34 (s, 1 H, OH). ^{1}H NMR (DMSO-d_6), δ: 3.38 (s, 3 H, Me); 6.67 (s, 1 H, H(5)); 6.99 (t, 1 H, H(5′), *J* = 7.5 Hz); 7.02 (d, 1 H, H(3′), *J* = 8.3 Hz); 7.32 (dd, 1 H, H(6′), *J* = 7.5 Hz, *J* = 1.6 Hz); 7.43 (ddd, 1 H, H(4′), *J* = 8.3 Hz, *J* = 7.5 Hz, *J* = 1.6 Hz); 10.48 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −64.6 (s, CF_3). ^{13}C NMR (DMSO-d_6), δ: 34.8 (Me), 97.0 (q, C(3), $^3J_{C,F}$ = 2.2 Hz), 103.8 (q, C(5), $^3J_{C,F}$ = 4.4 Hz), 113.4 (CN), 116.0 (C(3′)), 119.7 (C(5′)), 120.7 (C(1′)), 121.1 (q, CF_3, $^1J_{C,F}$ = 275.8 Hz), 129.8 (C(6′)), 132.5 (C(4′)), 143.9 (q, C(4), $^2J_{C,F}$ = 33.0 Hz), 154.3 (C(2′)), 156.7 (C(6)), 160.1 (C(2)).

6-(2-Hydroxy-5-methylphenyl)-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (4f). The yield was 85%, greenish crystals, m.p. 267—268 °C. Found (%): C, 58.28; H, 3.60; N, 9.11. $C_{15}H_{11}F_3N_2O_2$. Calculated (%): C, 58.45; H, 3.60; N, 9.09. IR, ν/cm^{-1}: 3221, 2233, 1635, 1613, 1598, 1572, 1556, 1508. ^{1}H NMR (DMSO-d_6), δ: 2.26 (s, 3 H, Me); 3.36 (s, 3 H, MeN); 6.66 (s, 1 H, H(5)); 6.91 (d, 1 H, H(3′), *J* = 8.4 Hz); 7.13 (d, 1 H, H(6′), *J* = 1.8 Hz); 7.23 (dd, 1 H, H(4′), *J* = 8.4 Hz, *J* = 1.8 Hz); 10.21 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −64.0 (s, CF_3).

6-(2-Hydroxy-4,6-dimethylphenyl)-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (4g). The yield was 88%, colorless crystals, m.p. 244—245 °C. Found (%): C, 59.21; H, 4.07; N, 8.59. $C_{16}H_{13}F_3N_2O_2$. Calculated (%): C, 59.63; H, 4.07; N, 8.69. IR, ν/cm^{-1}: 3357, 2239, 1649, 1618, 1581, 1553. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, Me(4′)); 2.26 (s, 3 H, Me(6′)); 3.28 (s, 3 H, MeN); 6.65 (s, 1 H, H(5)); 6.67 (s, 1 H, H(3′)); 6.68 (s, 1 H, H(5′)); 10.03 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −63.9 (s, CF_3).

6-(2-Hydroxy-5-nitrophenyl)-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (4h). The yield was 88%, beige crystals, m.p. 261—262 °C. Found (%): C, 49.50; H, 2.45. $C_{14}H_8F_3N_3O_4$. Calculated (%): C, 49.57; H, 2.38. IR, ν/cm^{-1}: 3091, 2233, 1641, 1617, 1573, 1558, 1527, 1492, 1338. ^{1}H NMR (DMSO-d_6), δ: 3.36 (s, 3 H, MeN); 6.87 (s, 1 H, H(5)); 7.18 (d, 1 H, H(3′), *J* = 9.0 Hz); 8.31 (d, 1 H, H(6′), *J* = 2.8 Hz); 8.34 (dd, 1 H, H(4′), *J* = 9.0 Hz, 2.8 Hz); 12.0—12.2 (br.s, 1 H, OH).

4-Difluoromethyl-6-(2-hydroxy-5-methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (4i). The yield was 95%,

orange crystals, m.p. 267—268 °C. Found (%): C, 61.94; H, 3.97; N, 9.70. $C_{15}H_{12}F_2N_2O_2$. Calculated (%): C, 62.07; H, 4.17; N, 9.65. IR, ν/cm^{-1}: 3190, 2226, 1633, 1612, 1597, 1573, 1552, 1509. ^{1}H NMR (DMSO-d_6), δ: 2.25 (s, 3 H, Me); 3.33 (s, 3 H, MeN); 6.48 (s, 1 H, H(5)); 6.90 (d, 1 H, H(3′), J = 8.3 Hz); 7.10 (d, 1 H, H(6′), J = 1.7 Hz); 7.14 (t, 1 H, CF_2H, J = 53.6 Hz); 7.22 (dd, 1 H, H(4′), J = 8.3 Hz, J = 1.7 Hz); 10.16 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −118.2 (dd, 1 F, C<u>F</u>FH, J = 310.0 Hz, J = 53.6 Hz); −117.2 (dd, 1 F, CF<u>F</u>H, J = 310.0 Hz, J = 53.6 Hz).

4-Difluoromethyl-6-(2-hydroxy-4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (4j). The yield was 80%, red crystals, m.p. 217—218 °C. Found (%): C, 58.67; H, 3.81; N, 9.19. $C_{15}H_{12}F_2N_2O_3$. Calculated (%): C, 58.83; H, 3.95; N, 9.15. IR, ν/cm^{-1}: 3279, 2223, 1644, 1613, 1577, 1555, 1518. ^{1}H NMR (DMSO-d_6), δ: 3.34 (s, 3 H, MeN); 3.78 (s, 3 H, MeO); 6.46 (s, 1 H, H(5)); 6.54 (d, 1 H, H(3′), J = 2.4 Hz); 6.58 (dd, 1 H, H(5′), J = 8.5 Hz, J = 2.4 Hz); 7.14 (t, 1 H, CF_2H, J = 53.7 Hz); 7.23 (d, 1 H, H(6′), J = 8.5 Hz); 10.48 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −118.2 (dd, 1 F, C<u>F</u>FH, J = 310.0 Hz, J = 53.7 Hz); −117.2 (dd, 1 F, CF<u>F</u>H, J = 310.0 Hz, J = 53.7 Hz).

6-(2-Hydroxy-4-methoxyphenyl)-1-methyl-2-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,2-dihydropyridine-3-carbonitrile (4k). The yield was 78%, orange crystals, m.p. 249—250 °C. Found (%): C, 53.62; H, 3.27; N, 7.83. $C_{16}H_{12}F_4N_2O_3$. Calculated (%): C, 53.94; H, 3.39; N, 7.86. IR, ν/cm^{-1}: 3248, 2232, 1642, 1613, 1578, 1548, 1518. ^{1}H NMR (DMSO-d_6), δ: 3.37 (s, 3 H, MeN); 3.78 (s, 3 H, MeO); 6.42 (s, 1 H, H(5)); 6.55 (d, 1 H, H(3′), J = 2.3 Hz); 6.60 (dd, 1 H, H(5′), J = 8.5 Hz, J = 2.3 Hz); 6.90 (tt, 1 H, $(CF_2)_2H$, J = 51.7 Hz, J = 4.0 Hz); 7.24 (d, 1 H, H(6′), J = 8.5 Hz); 10.53 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −136.3 (dt, 2 F, CF_2H, J = 51.7 Hz, J = 5.5 Hz); −116.0 (q, 2 F, CF_2, J = 5.5 Hz).

6-(2-Hydroxy-4-methoxyphenyl)-1-methyl-2-oxo-4-perfluoroethyl-1,2-dihydropyridine-3-carbonitrile (4l). The yield was 75%, orange crystals, m.p. 208—209 °C. Found (%): C, 51.25; H, 2.86; N, 7.48. $C_{16}H_{11}F_5N_2O_3$. Calculated (%): C, 51.35; H, 2.96; N, 7.48. IR, ν/cm^{-1}: 3292, 2235, 1639, 1615, 1581, 1551, 1517. ^{1}H NMR (DMSO-d_6), δ: 3.38 (s, 3 H, MeN); 3.78 (s, 3 H, MeO); 6.53 (s, 1 H, H(5)); 6.55 (s, 1 H, H(3′)); 6.60 (d, 1 H, H(5′), J = 8.5 Hz); 7.24 (d, 1 H, H(6′), J = 8.5 Hz); 10.54 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −115.3 (s, 2 F, CF_2); −83.4 (s, 3 F, CF_3).

3-Acetyl-6-(2-hydroxyphenyl)-4-trifluoromethyl-1-phenylpyridin-2(1*H*)-one (4m). The yield was 38%, colorless crystals, m.p. 216—217 °C. Found (%): C, 64.46; H, 3.57; N, 3.85. $C_{20}H_{14}F_3NO_3$. Calculated (%): C, 64.34; H, 3.78; N, 3.75. IR, ν/cm^{-1}: 3140, 1713, 1644, 1601, 1572, 1556, 1502, 1490. ^{1}H NMR (DMSO-d_6), δ: 2.48 (s, 3 H, Me); 6.35 (s, 1 H, H(5)); 6.60—6.65 (m, 2 H, H(5′), H(3′)); 6.98—7.04 (m, 2 H, H(4′), H(6′)); 7.12—7.27 (m, 5 H, Ph); 9.71 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −61.7 (s, CF_3).

6-(2-Hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (6a). The yield was 60%, light yellow crystals, m.p. 307—308 °C. Found (%): C, 67.59; H, 3.83; N, 12.86. $C_{12}H_8N_2O_2$. Calculated (%): C, 67.92; H, 3.80; N, 13.20. IR, ν/cm^{-1}: 2225, 1644, 1574, 1558. ^{1}H NMR (DMSO-d_6), δ: 6.63 (br.s, 1 H, H(5)); 6.93 (td, 1 H, H(5′), J = 7.4 Hz, J = 0.8 Hz); 6.99 (dd, 1 H, H(3′), J = 8.2 Hz, J = 0.8 Hz); 7.35 (ddd, 1 H, H(4′), J = 8.2 Hz, J = 7.4 Hz, J = 1.7 Hz); 7.49 (br.s, 1 H, H(6′)); 8.15 (d, 1 H, H(4), J = 7.6 Hz); 10.3—10.8 (br.s, 1 H, OH); 12.2—12.6 (br.s, 1 H, NH/OH).

6-(2-Hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6b). The yield was 47%, light brown crystals, m.p. 280—281 °C. Found (%): C, 67.70; H, 4.65; N, 11.89. $C_{13}H_{10}N_2O_2 \cdot 0.25H_2O$. Calculated (%): C, 67.67; H, 4.59; N, 12.14. IR, ν/cm^{-1}: 2226, 1626, 1601, 1553, 1500. ^{1}H NMR (DMSO-d_6), δ: 3.28 (s, 3 H, Me); 6.30 (d, 1 H, H(5), J = 7.5 Hz); 6.96 (td, 1 H, H(5′), J = 7.6 Hz, J = 1.0 Hz); 7.00 (dd, 1 H, H(3′), J = 8.2 Hz, J = 0.9 Hz); 7.24 (dd, 1 H, H(6′), J = 7.6 Hz, J = 1.7 Hz); 7.38 (ddd, 1 H, H(4′), J = 8.2 Hz, J = 7.6 Hz, J = 1.7 Hz); 8.13 (d, 1 H, H(4), J = 7.5 Hz); 10.30 (s, 1 H, OH).

6-(2-Hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (6c). The yield was 32%, light yellow crystals, m.p. 306—307 °C. Found (%): C, 62.50; H, 4.50. $C_{12}H_{10}N_2O_3$. Calculated (%): C, 62.60; H, 4.38. IR, ν/cm^{-1}: 3367, 3143, 1668, 1575, 1556. ^{1}H NMR (DMSO-d_6), δ: 6.68 (br.s, 1 H, H(5)); 6.93 (td, 1 H, H(5′), J = 7.6 Hz, J = 1.0 Hz); 6.99 (d, 1 H, H(3′), J = 8.2 Hz); 7.33 (ddd, 1 H, H(4′), J = 8.2 Hz, J = 7.6 Hz, J = 1.7 Hz); 7.47 (br.d, 1 H, NH); 7.52 (br.s, 1 H, H(6′)); 8.34 (d, 1 H, H(4), J = 7.6 Hz); 9.09 (br.s, 1 H, NH); 10.4—10.6 (br.s, 1 H, OH); 12.1—12.3 (br.s, 1 H, NH/OH).

6-(2-Hydroxy-5-nitrophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6d). The yield was 71%, light brown crystals, m.p. >330 °C. Found (%): N, 15.25. $C_{13}H_9N_3O_4$. Calculated (%): N, 15.49. IR, ν/cm^{-1}: 2230, 1651, 1605, 1528. ^{1}H NMR (DMSO-d_6), δ: 2.47 (s, 3 H, Me); 6.87 (br.s, 1 H, H(5)); 7.10 (d, 1 H, H(3′), J = 9.1 Hz); 8.16 (dd, 1 H, H(4′), J = 9.1 Hz, J = 2.7 Hz); 8.42 (br.s, 1 H, H(6′)); 11.0—13.2 (br.s, 2 H, NH, OH).

6-(2-Hydroxy-5-nitrophenyl)-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6e). The yield was 69%, light brown crystals, m.p. >330 °C. Found (%): C, 58.91; H, 4.08; N, 14.71. $C_{14}H_{11}N_3O_4$. Calculated (%): C, 58.95; H, 3.89; N, 14.73. IR, ν/cm^{-1}: 2229, 1614, 1563, 1549, 1489. ^{1}H NMR (DMSO-d_6), δ: 2.40 (s, 3 H, Me); 3.23 (s, 3 H, MeN); 6.42 (s, 1 H, H(5)); 7.17 (d, 1 H, H(3′), J = 9.0 Hz); 8.21 (d, 1 H, H(6′), J = 2.7 Hz); 8.31 (dd, 1 H, H(4′), J = 9.0 Hz, J = 2.7 Hz); 11.98 (s, 1 H, OH).

6-(2-Hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (6f). The yield was 37%, beige crystals, m.p. 251—252 °C. Found (%): C, 63.86; H, 4.74; N, 11.41. $C_{13}H_{12}N_2O_3$. Calculated (%): C, 63.93; H, 4.95; N, 11.47. IR, ν/cm^{-1}: 1684, 1619, 1575, 1517. ^{1}H NMR (DMSO-d_6), δ: 2.40 (s, 3 H, Me); 6.42 (br.s, 1 H, H(5)); 6.90 (td, 1 H, H(5′), J = 7.6 Hz, J = 1.0 Hz); 6.95 (d, 1 H, H(3′), J = 8.3 Hz); 7.29 (ddd, 1 H, H(4′), J = 8.3 Hz, J = 7.0 Hz, J = 1.6 Hz); 7.2—7.6 (br.s, 2 H, H(6′), NH); 8.55 (br.s, 1 H, NH); 10.40 (br.s, 1 H, OH); 11.72 (br.s, 1 H, NH/OH).

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